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EXAMINER

STRZELECKA, TERESA E

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/606,502

Applicant(s)

MARTIENSSEN ET AL.

Examiner

Teresa E. Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 107,110,111 and 116-133 is/are pending in the application.
- 4a) Of the above claim(s) 110,125-128,130 and 131 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 107,111,116-124,129,132 and 133 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. <u>3/27/06</u> . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/28/04; 2/1/05; 10/20/05; 1/23/06</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 107-133; species of claims 112, 115-117, 129, 132, 133, 120, 121, 123 and 124) in the reply filed on January 23, 2006 is acknowledged. The traversal is on the ground(s) that

A) the search for Group I and II would not constitute an undue burden and that examiner must examine claims on the merits if there is no undue burden. Applicants cite MPEP 803.01 to support this view. This is not found persuasive because, first, as explained in the Requirement for Election/Restriction mailed December 23, 2005, the claims of Group II were drawn to a polynucleotide on a solid support, which can be used in a multitude of methods, not necessarily the method claimed in Group I, and which encompass bead-bound single hybridization probes, arrays of polynucleotides and oligonucleotides, etc. Therefore, finding a reference teaching a solid support with a polynucleotide bound to it would not result in finding a reference teaching the method of Group I. Further, it seems that the MPEP paragraph cited by Applicants is not related to the issue of search burden as it states:

**803.01 Review by Examiner with at Least Partial Signatory Authority [R-3] -
800 Restriction in Applications Filed Under 35 U.S.C. 111; Double Patenting**

803.01 Review by Examiner with at Least Partial Signatory Authority [R-3]

Since requirements for restriction under 35 U.S.C. 121 are discretionary with the *>Director<, it becomes very important that the practice under this section be carefully administered. Notwithstanding the fact that this section of the statute apparently protects the applicant against the dangers that previously might have resulted from compliance with an improper requirement for restriction, IT STILL REMAINS IMPORTANT FROM THE STANDPOINT OF THE PUBLIC INTEREST THAT NO REQUIREMENTS BE MADE WHICH MIGHT RESULT

IN THE ISSUANCE OF TWO PATENTS FOR THE SAME INVENTION.

Therefore, to guard against this possibility, only an examiner with permanent >full signatory authority< or temporary full signatory authority may sign final ** Office actions containing a final requirement for restriction**>. An< examiner with permanent >partial signatory authority< or temporary partial signatory authority may sign non-final Office actions containing a final requirement for restriction.

B) Regarding the election of species, Applicants argue that there is no necessity for election of species in claims 123-131, since these steps are not performed in the independent claim 107, and the steps of claim 107 can be performed without these claims.

Examiner agrees with Applicants that claim 107 does not require any of the claims 123-131. However, these claims constitute additional method steps which are quite different from each other, necessitating the election of species requirement. In principle all of these claims could have been placed in separate groups, however, for the sake of Applicants' convenience, were made to be separate species, with claim 107 being a linking claim. As these additional method steps are divergent in their methodology, the restriction is proper. Once the linking claim becomes allowable, the remaining unexamined species would be rejoined with the examined ones.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 110, 125-128, 130 and 131 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 23, 2006.
3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any

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amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claims 107-137 were previously pending. Applicants cancelled claims 108, 109, 112-115 and 134-137, and amended claims 107, 116-120. Claims 107, 111, 116-124, 129, 132 and 133 will be examined.

Information Disclosure Statement

5. The information disclosure statements (IDSs) submitted on May 28, 2004, February 1, 2005 and October 20, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner, with the exception of references AA-AE of the October 20, 2005 IDS, which do not have the date and place of publication.

6. The information disclosure statement (IDS) submitted on January 23, 2006 was filed after the mailing date of the Election/Restriction Requirement on December 23, 2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 107, 116-124, 129, 132 and 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 107, 116-124, 129, 132 and 133 are indefinite in claim 107. Claim 107 is indefinite because the claim does not recite a final process step which clearly relates back to the preamble. The

preamble states that the method is for “determining a methylation profile of a cell, tissue or organism”, but the final process step is “quantifying the relative amount of at least one sequence from at least two of the following..”. Therefore, it is unclear as to whether the claim is intended to be limited to a method of determining a methylation profile or a method of quantifying the relative amounts of methylated or unmethylated sequences.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 107, 111, 116, 117, 119-124, 129, 132 and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (Hum. Mol. Genet., vol. 8, pp. 459-470, 1999; cited in the IDS) and Oefner et al. (Nucl. Acids Res., vol. 24, pp. 3879-3886, 1996).

A) Regarding claim 107, Huang et al. teach a method of determining a methylation profile of cells or tissues (Abstract), the method comprising:

a. providing a population of randomly cleaved or sheared DNA fragments from the cell, tissue, or organism, wherein the DNA comprises a first portion and a second portion and each portion comprises methylated and unmethylated fragments (Huang et al. teach providing a population of restriction-enzyme fragmented DNA from normal breast tissue and breast cancer cells. The first portion of the DNA, which contains methylated and unmethylated fragments, is not further digested, whereas the second portion is digested with the BstU I restriction enzyme (Fig. 2; page 468, second paragraph).);

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b. depleting methylated or unmethylated DNA from the second-portion (Huang et al. teach depleting the unmethylated DNA from the second portion by digesting the DNA with BstU I enzyme which degrades unmethylated DNA (Fig. 2; page 468, second paragraph).); and

c. quantifying the relative amount of at least one sequence from at least two of the following:

the first portion,

methylated DNA in the second portion, and

unmethylated DNA in the second portion (Huang et al. teach quantifying the relative amount of DNA from the first portion and methylated second portion (Fig. 2; page 468, last paragraph; page 469, third paragraph; Fig. 4-7; page 461, second, third and last paragraphs; page 463; page 467, first paragraph).).

Regarding claim 111, Huang et al. teach the average size of DNA fragments of 10-200 bp (= 0.1-0.2 kb) (page 460, third paragraph).

Regarding claims 116 and 132, Huang et al. teach digesting the DNA with BstU I enzyme which degrades unmethylated DNA (Fig. 2; page 468, second paragraph).

Regarding claims 117 and 133, Huang et al. teach labeling the first and second portions with a label and hybridizing these two portions to nucleic acid probes to determine relative methylation of the first and second portions (Fig. 2; page 468, last paragraph; page 469, third paragraph; Fig. 4-7; page 461, second, third and last paragraphs; page 463; page 467, first paragraph).

Regarding claim 119, Huang et al. teach digesting the DNA with BstU I enzyme which degrades unmethylated DNA (Fig. 2; page 468, second paragraph).

Regarding claim 120, Huang et al. teach hybridization of the DNA depleted in unmethylated fragments to a nucleic acid linked to a solid support (Fig. 2; page 468, last paragraph; page 469,

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third paragraph; Fig. 4-7; page 461, second, third and last paragraphs; page 463; page 467, first paragraph).

Regarding claim 121, Huang et al. teach a solid support being a microarray on a membrane (Fig. 2, 4, 5), according to Applicants' definition in paragraph [81] of the specification.

Regarding claim 122, Huang et al. teach human samples, therefore they inherently teach animal samples (page 467, last paragraph).

Regarding claim 123, Huang et al. teach comparing the methylation profile with the transcription profile of nucleic acids (page 468, first paragraph; Fig. 1; page 460, second and third paragraphs; page 461, last paragraph; page 462, first paragraph; page 463; page 464, first paragraph).

Regarding claim 124, Huang et al. teach detection of the expression profile using a Northern blot (page 468, first paragraph). Since the Northern blot contains an ordered arrangement of hybridizable elements (as defined by Applicants in paragraph [81]), Huang et al. inherently teach a microarray.

Regarding claim 129, Huang et al. teach two different DNA samples, one containing normal breast tissue and the other breast cancer cells, depleting unmethylated DNAs from both samples and comparing the amounts of sequences from the fractions of first and second samples (Fig. 4; page 461, second, third and last paragraphs; page 462, first paragraph; 468, last paragraph).

B) Huang et al. teach fragmentation of DNA using a restriction enzyme, but do not teach random fragmentation or shearing to obtain the DNA fragments.

C) Oefner et al. teach random fragmentation of DNA using by shearing using hydrodynamic shearing mode (page 3880, second paragraph; page 3881, last paragraph; page 3882, first, second and third paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used DNA fragmentation by shearing of Oefner et al. in the method of Huang et al. The motivation to do so, provided by Oefner et al., would have been that fragments with few restriction sites are underrepresented in restriction digests (page 3879, first paragraph), the hydrodynamic shear provided control over the size of the sheared fragments (page 3882, second paragraph; Fig. 2) and the size distribution was independent on the type of DNA used (page 3882, third paragraph).

11. Claim 118 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (Hum. Mol. Genet., vol. 8, pp. 459-470, 1999; cited in the IDS) and Oefner et al. (Nucl. Acids Res., vol. 24, pp. 3879-3886, 1996) as applied to claim 107 above, and further in view of Bestor (US 2003/0099997 A1; cited in the IDS).

A) The teachings of Huang et al. and Oefner et al. are presented above. Neither reference teaches depleting methylated DNA from the sample.

B) Bestor teaches determination of differential methylation between two different sources by depleting methylated DNA from one of the samples (page 2, [0013]-[0021]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used depletion of methylated sequences of Bestor in the method of Huang et al. and Oefner et al. The motivation to do so, provided by Bestor, would have been that, as stated by Bestor (page 6, [0073]):

“One of the difficulties in analyzing tumor samples, for instance, is that the tumors themselves are often a heterogeneous mix of wild-type and cancerous cells. MSA has been designed so that methylated sequences from disease cells will be enzymatically removed from unmethylated genomic libraries derived from normal tissue while unmethylated sequences will be enzymatically

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removed from methylated libraries derived from disease tissue. This allows for accurate identification of genomic loci that display differential methylation between the normal and disease tissues.”

12. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**TERESA STRZELECKA
PATENT EXAMINER**

Teresa Strzelecka
3/31/06